role of the skin in immunologic processes. Cutaneous involvement in immune processes occurs at many levels and comprises both cellular and humoral components operating in a complex interplay of signals and responses. Discoveries concerning physiologic properties of the skin immune system have led to important advances in our understanding of both normal and disease events that occur in the skin and other tissues. The overlapping arenas of cell biology, immunology, and directed therapeutics have found fertile ground in the skin and in dermatologic diseases. We can expect that continued advances in the understanding of these processes in both normal and diseased skin will lead to novel therapeutic modalities for a growing number of dermatologic diseases in the coming years.

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Low-Density Lipoprotein Oxidation and the Pathogenesis of Atherosclerosis

THE EPIDEMIOLOGIC ASSOCIATION of low-density lipoprotein (LDL) and coronary heart disease (CHD) has been amply and repeatedly documented. Moreover, clinical trials have clearly demonstrated that clinical manifestations of CHD can be reduced by therapies that reduce LDL-cholesterol levels.[1] Angiographic studies show that the progression of atherosclerotic lesions can be inhibited and lesions can even regress when LDL-cholesterol concentrations are markedly reduced by diet[2] and drug therapy.[3-5] These findings strongly implicate LDL in the pathogenesis of atherosclerosis. But the mechanisms by which LDL damages arterial walls have remained elusive until recently. During the past several years there has been a dramatic increase in our understanding of the mechanisms by which LDL influences the process of atherogenesis. Studies in animals and using human atherosclerotic lesions have provided important insights into the pathogenesis of atherosclerosis in general and about the role of lipoproteins in particular. An important culprit appears to be the oxidation of LDL.

As thoroughly reviewed in the article by Young and Parthasarathy in this issue of the journal,[6] oxidized LDL affects many of the biologic events that occur as atherosclerotic lesions develop and progress. Early studies focused on cellular lipid metabolism, where oxidized LDL has been shown to be taken up by macrophage scavenger receptors and to lead to lipid accumulation, one of the hallmarks of all stages of atherosclerosis. More recent studies have shown that oxidized LDL can be involved in virtually every process of atherosclerosis. Thus, as described in the accompanying article, studies have shown that this modified lipoprotein can stimulate the adhesion of monocytes to endothelial cells and stimulate monocyte chemotaxis, both directly and by inducing the expression of chemotactic factors such as monocyte chemotactic protein 1. T-lymphocyte chemotaxis has recently been shown to be stimulated. These all are early events during the formation of fatty streaks. Oxidized LDL also modulates the expression of growth factors and cytokines that are thought to play a pathogenic role later during atherosclerosis, to influence vascular reactivity, and to stimulate the expression of molecules involved in thrombogenesis, another important component of the atherogenic process.

The observation that several of these events can be influenced by LDL that has undergone only mild oxidative changes is of considerable interest because it suggests that some oxidized lipids formed early during LDL modification can influence gene expression. These pleiotropic effects of oxidized LDL have largely been demonstrated in vitro and have led to the generation of a model whereby the oxidation of LDL plays a central role in the pathogenesis of atherosclerosis.[7,8] In this model, LDL that enters the subendothelial space by transcytosis undergoes mild oxidative changes mediated by endothelial cells. This mildly oxidized form of LDL stimulates the expression of genes such as endothelial adhesion molecules, chemotactic factors and colony-stimulating factors, which result in the attraction, retention, maturation, and activation of monocyte or macrophages and T lymphocytes. With time the LDL becomes more extensively oxidized by macrophages and smooth muscle cells that migrate from the media. Extensively oxidized LDL can lead to macrophage foam cell formation and is cytotoxic. Oxidized LDL also can stimulate the expression of molecules that favor thrombogenesis, which can precipitate clinical events.

Although this model has been generated largely on the basis of experiments performed in vitro, lipoproteins with many of the features of oxidized LDL have been isolated from atherosclerotic lesions.[9] Oxidation-specific epitopes using antibodies generated against oxidized LDL also are present in lesions from both animals and humans.[10,11] Circulating antibodies that recognize oxidized LDL also

have been demonstrated.[11] Thus, there is good evidence for the occurrence of oxidatively modified lipoproteins in vivo. Although several plausible mechanisms for the oxidation of LDL by cells of the artery wall have been described in vitro, the precise mechanism (or mechanisms) by which LDL is oxidized in vivo remains uncertain. Nevertheless, emerging evidence suggests that lipoprotein oxidation may be involved in atherogenesis in several situations associated with increased atherosclerosis risk. These include cigarette smoking,[12] diabetes mellitus,[13] and the atherogenic lipoprotein phenotype that is characterized by the presence of small, dense LDLs.[14] Clinical evaluation of lipoprotein oxidation is difficult because this process is likely to occur in the milieu of the artery wall rather than in the circulation.[15] Thus, investigation of this process in humans has to rely on indirect measures,[15] which are unlikely to be of widespread clinical use.

If lipoprotein oxidation is so important in atherogenesis, then measures that limit this process should be useful in preventing it. As clearly pointed out by Young and Parthasarathy, the role of antioxidants in the prevention of atherosclerosis is supported by several lines of evidence.[6] Perhaps the most convincing evidence comes from studies of animals, where the administration of several antioxidants—probucol, butylated hydroxytoluene, diphenyl phenyldiamene, and vitamin E—has ameliorated the formation of atherosclerotic lesions.[16] Because most of these studies have been done in rabbits, additional data from other atherosclerosis-prone species would be valuable. There also is reasonably strong epidemiologic evidence that the level of consumption of antioxidant vitamins, especially vitamin E, is inversely associated with CHD risk.[17] Two recent large prospective studies suggest that vitamin E protection against the development of CHD is achieved only at doses in excess of those attainable by diet alone.[18,19] Clinical studies also have shown that high doses of vitamin E are required to render circulating LDL relatively resistant to oxidative modification.[20,21] Thus, vitamin supplementation may be the only way that LDL can be protected from oxidative modification. Which vitamins to use, the appropriate doses, and possible side effects remain to be determined.

To date, no placebo-controlled clinical trials have been done using natural antioxidants. The results of a recently completed clinical trial that evaluated the effect of the powerful antioxidant, probucol, on femoral angiographic end points are awaited with interest. Carefully controlled clinical trials of the effect of supplementation with natural antioxidants clearly are needed before their use can be widely recommended in the prevention of CHD. In the meantime, one way of limiting the oxidation of LDL in the artery wall is to keep plasma LDL-cholesterol levels low, a strategy that has been tried and tested and shown to be of benefit.

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